Applicants : B. PFEIFFER
Y-M GINOT
G. COQUEREL
S. BEILLES

Serial N°: 10/792,355

Filed : March 3, 2004

Title : New alpha crystalline form of perindopril tert-butylamine salt

Art Unit : 1626

Examiner : SHIAO

Honorable Commissioner of Patents and Trademarks
Alexandria, V.A. 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, Gérard COQUEREL, a citizen of France, of 192, rue de l'Eglise, 76520 Boos, France, declare and say that :

I hold the degree of Doctor of University of Rouen, Faculty of Science, in 1986.

Since 1988, I have been Professor of solid state chemistry at the University of Rouen Mont-Saint-Aignan, France.

I am the author or co-author of more than 200 international publications such as patents, scientific publications, chapters of books and communications.

I am one of the co-inventors of US Patent Application Serial n° 10/792,355 filed March 3, 2004 concerning " New alpha crystalline form of perindopril tert-butylamine salt".

I am thoroughly familiar with the above-mentioned patent application and fully support the experiments contained therein which were performed either by me or under my supervision. I also fully support the conclusions derived therefrom and the arguments presented as concerns the novelty and inventive step of the crystalline form described.

Step 3D of US 4,914,214 has been reproduced with the use of rapid cooling (Experiment 1). The X-ray diffraction spectrum of the product obtained makes it possible to say that its structure does not correspond to the α structure and approaches that of a hydrated beta structure.

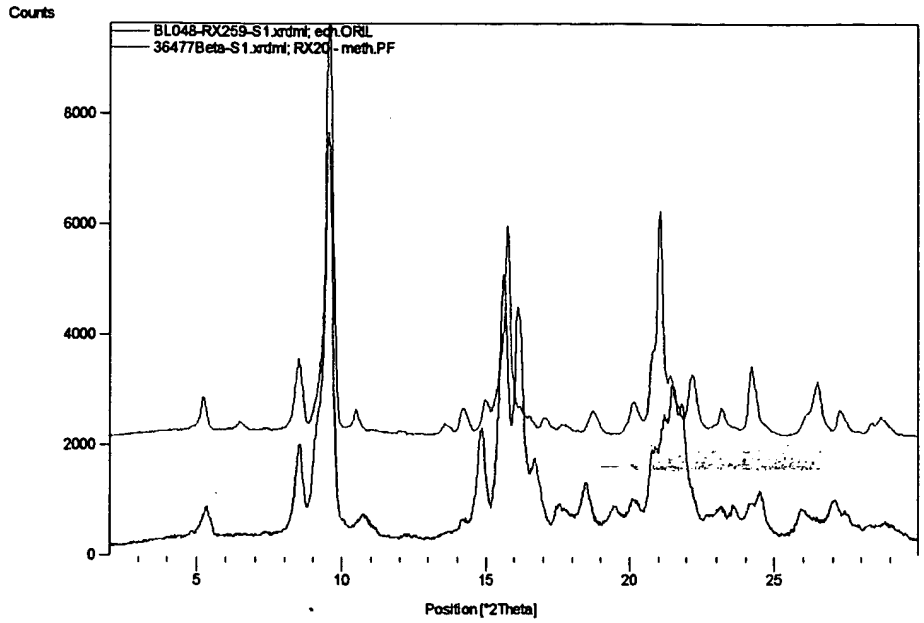
EXPERIMENT N°1

REPRODUCTION OF STEP 3D OF US 4,914,214

There are introduced into a reactor 14 ml of ethyl acetate and 1 g of (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(ethoxycarbonyl)-butylamino]-propionyl}-octahydro-1H-indole-2-carboxylic acid containing 2% of impurities. To the above mixture are added 2,2 g of tert-butylamine. The mixture is then brought to reflux until complete dissolution, filtered, cooled (rapid cooling to –15°C), filtered and dried at 40°C, to produce 0,83 g of product.

RX spectrum of the form obtained in experiment n°1

No.	Pos. [°2Th.]	Area [cts*°2Th.]	Normalized Area (%)	d-spacing [Å]
1	5,4	49	6,85	16,396
2	8,6	308	21,72	10,301
3	9,1	291	24,65	9,683
4	9,6	1774	100,00	9,238
5	10,7	54	4,55	8,230
6	14,2	27	1,88	6,224
7	14,9	389	23,53	5,958
8	15,6	947	61,58	5,665
9	16,3	386	46,67	5,449
10	16,7	186	15,70	5,294
11	17,6	66	4,68	5,042
12	18,5	132	10,19	4,784
13	19,5	63	3,34	4,546
14	20,1	54	4,53	4,411
15	20,8	154	16,24	4,267
16	21,2	230	24,37	4,185
17	21,5	392	33,12	4,125
18	21,9	222	26,88	4,055
19	23,2	62	3,78	3,838
20	23,6	50	4,21	3,766
21	24,6	109	9,23	3,623
22	25,9	114	5,34	3,434
23	27,1	134	7,10	3,287
24	27,4	62	4,39	3,249



The X-ray diffraction spectrum of the product obtained makes it possible to say that its structure does not correspond to the α structure and approaches that of a hydrated beta structure.

Therefore, the above experiment n°1 shows that the alpha form is not inherently disclosed in US 4,914,214.

EXPERIMENT N°2

COMPARED STABILITY

A study was made of the relative stability of the product obtained in Experiment n°1 and of the α form according to the invention, by studying the change over time in the IR spectra under normal storage conditions.

It can be seen that the α form according to the invention has improved stability over the form obtained by reproducing the process disclosed in Step 3D of US 4,914,214.

Stability over time of the α and β hydrated crystalline forms

Figure 1: stability over time of the compound obtained in Experiment n°1 in normal storage conditions

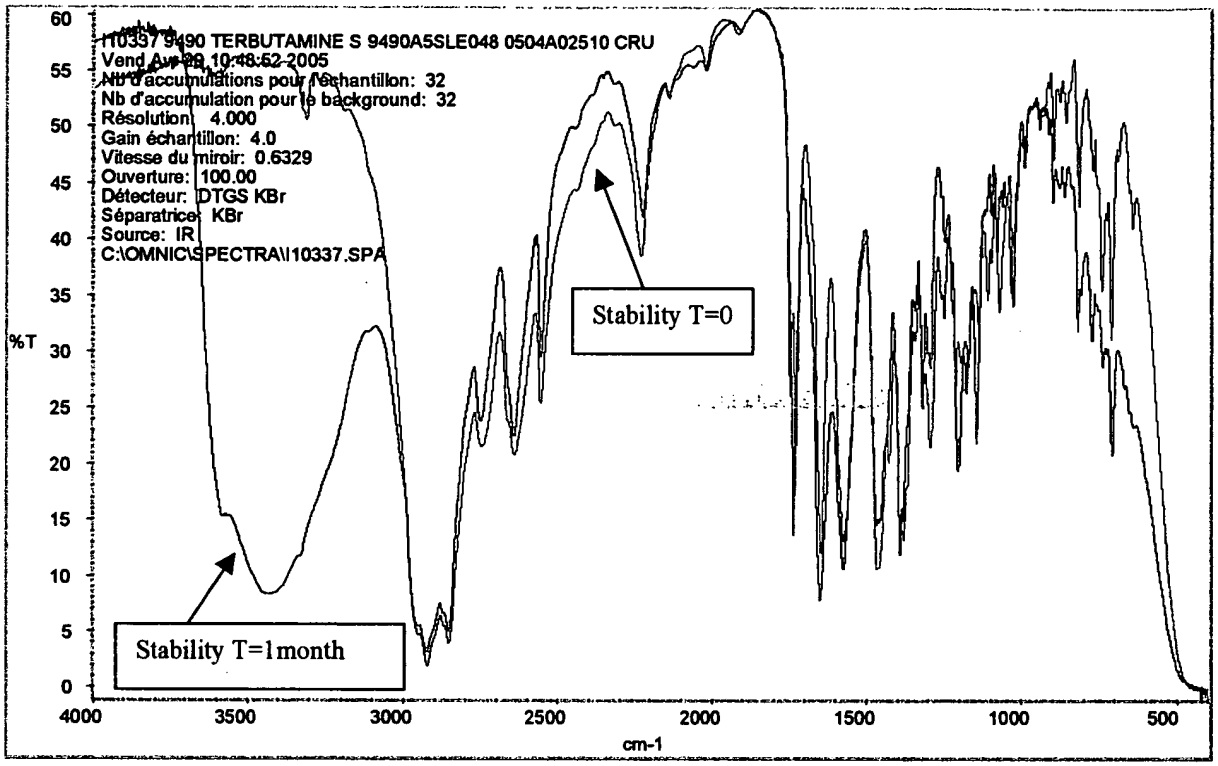
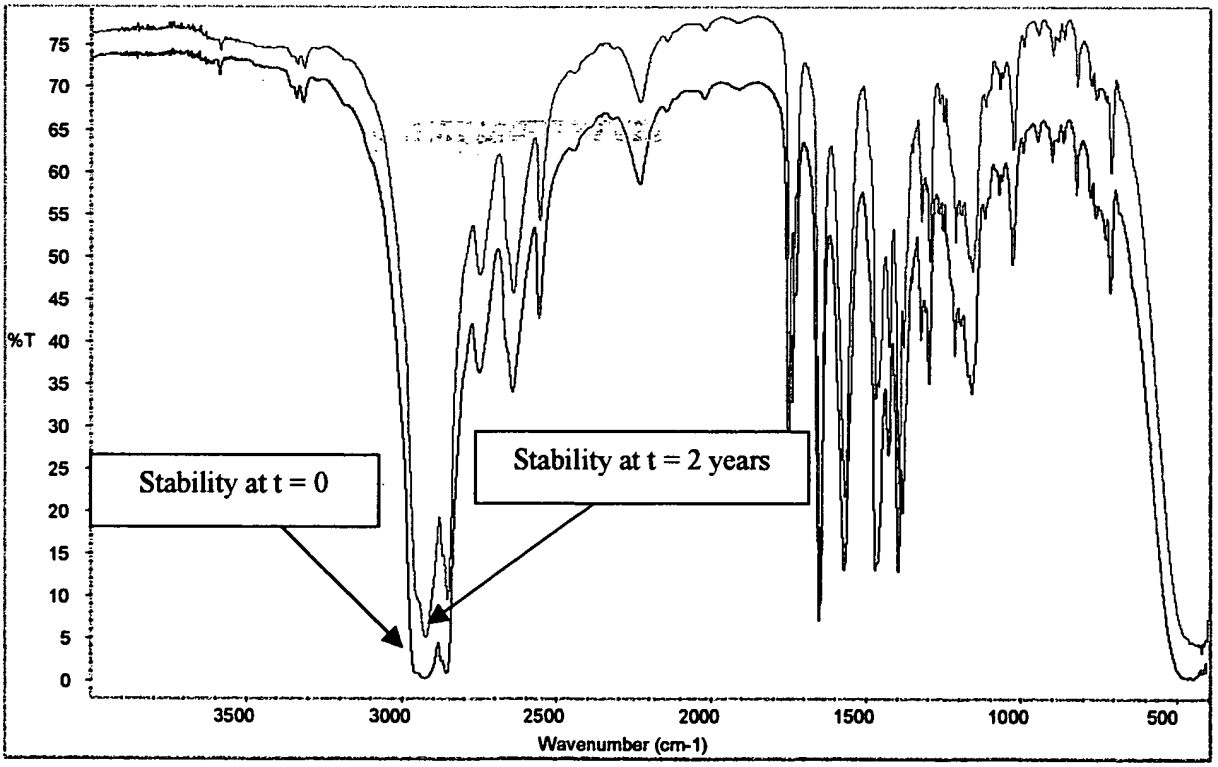


Figure 2: stability over time of the alpha form (normal storage conditions)



EXPERIMENT N°3
TEST OF FILTRATION

3a : Test in accordance with a method of active cooling according to US 4,914,214

A 100 litre reactor was used, the various components of Example 3D of patent specification US 4,914,214 being introduced into the reactor in amounts equal to half the indicated amounts.

The reaction mixture is heated to reflux and maintained at reflux for 30 minutes. Over 1 hour, cooling is carried out from the reflux temperature (= 75°C) to -10°C, or 85°C/h. The mixture is maintained at -10°C for 40 minutes. The suspension is filtered through an agitated enclosed filter.

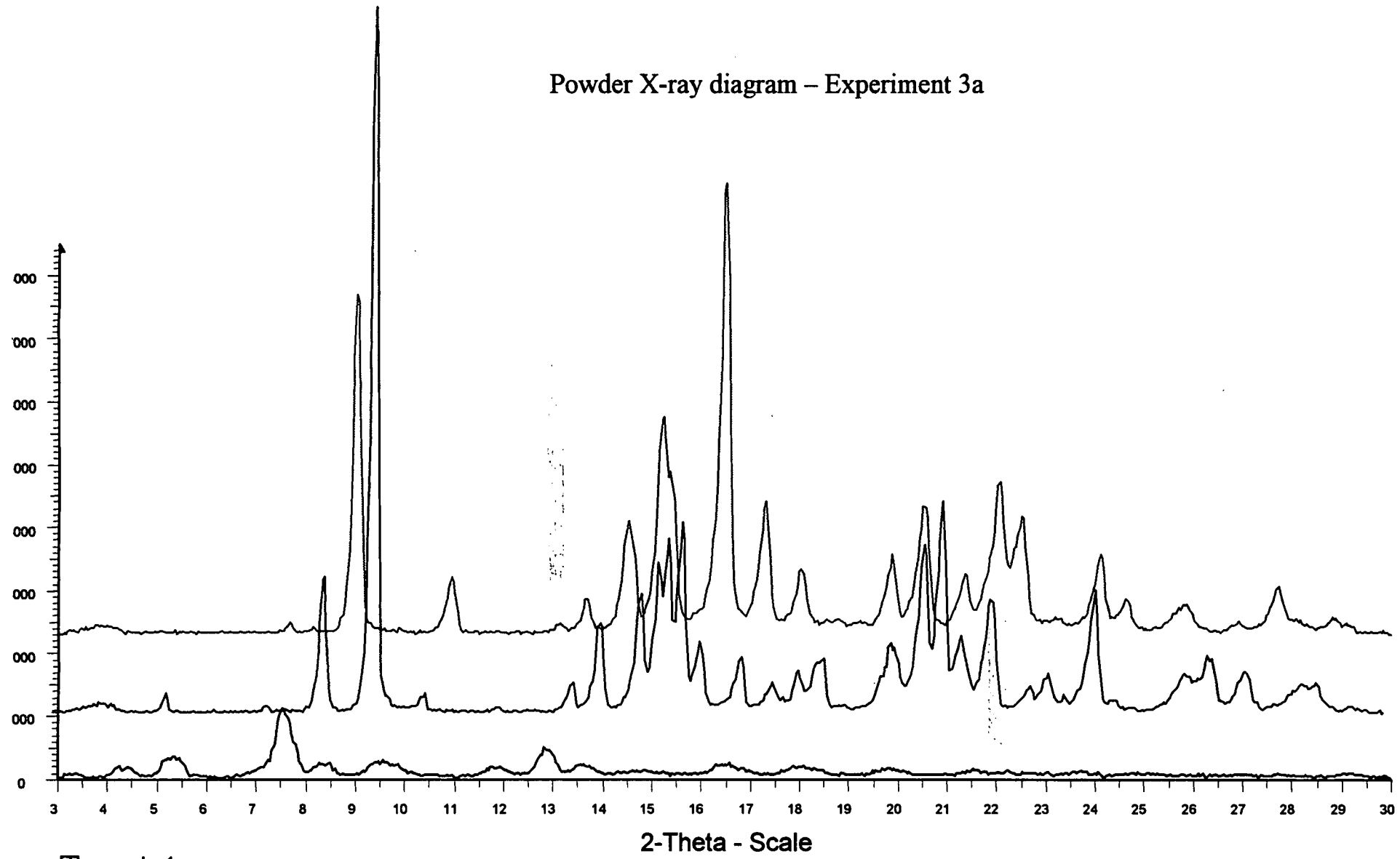
The filtration time is **15 hours**. The product is dried in an oven at 20°C for 48 hours.

Two successive samples are taken. The first sample is taken from the filter during drying; the second is taken after drying is complete.

An X-ray diffraction diagram is made of the products obtained; the diagrams are superimposed on the diagram of the α form.
The X-ray diagram confirms that the structure of both samples does not correspond to the α structure.

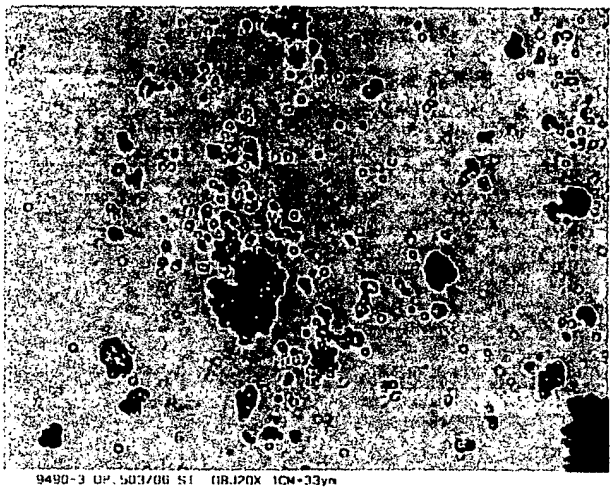
The product obtained in experiment 3a is also photographed. The photos show that it is not in the form of individual needles, but in the form of aggregates, which are very difficult to filtrate. This is confirmed by the filtration time of the product (15 hours).

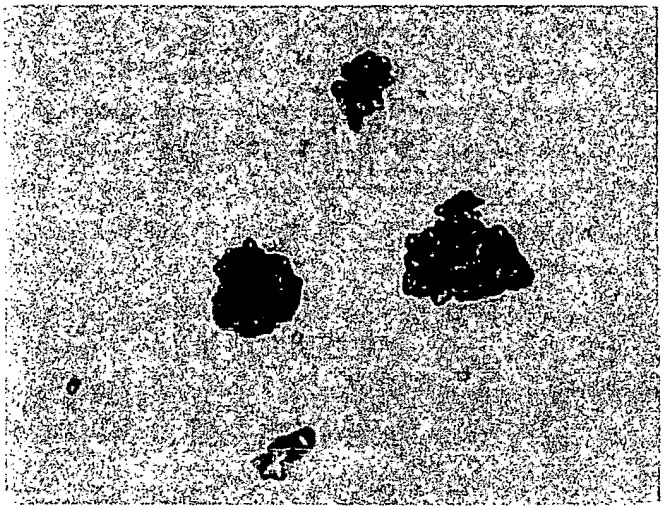
Powder X-ray diagram – Experiment 3a

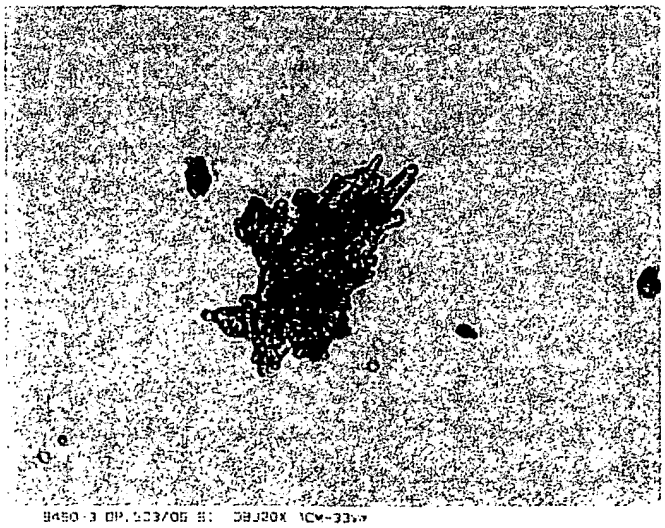


Photographs under a microscope of the powder obtained

in the experiment n°3a reproducing the process of US 4,914,214





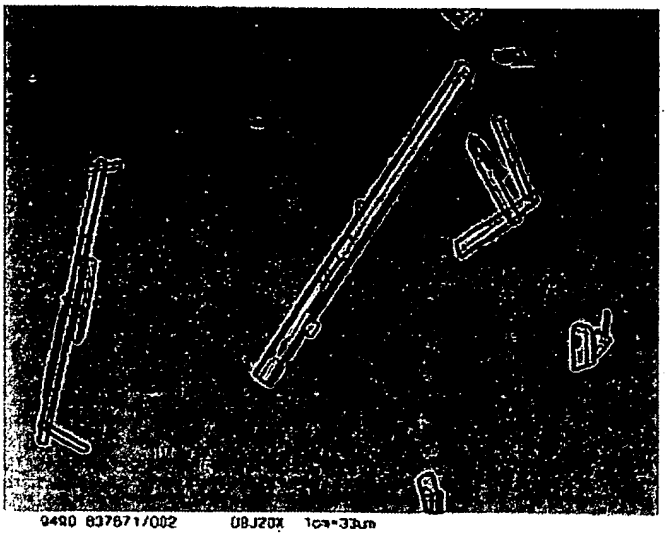


3b : For comparison purposes, proceeding as described in the patent specification of US Serial N° 10/792,355 :

Slowly cool the reaction mixture from the reflux temperature to 55°C in 3 hours 40 minutes (5.5°C/h). Allow to cool to 20°C (in 1 hour 40 minutes). Maintain at 20°C for 90 minutes. Filter the suspension through an agitated enclosed filter.

The filtration time is 7 **minutes**, which proves that the alpha form obtained is much easier to filtrate than the form obtained by reproducing the process disclosed in US 4,914,214.

Photographs under a microscope of the alpha form of perindopril tert-butylamine



I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of the title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not

Gérard Coquerel GC

Gérard COQUEREL

Executed at : Courbevoie

Date : July 28 ; 2006

Postal address :
LES LABORATOIRES SERVIER
12 place Défense
92415 COURBEVOIE CEDEX
FRANCE